Armed Forces College of Medicine

AFCM

Glucose Homeostasis in Different Organs

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Lecturer

Medical Biochemistry and molecular biology

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. **Interpret different regulatory mechanisms of the main metabolic pathways in different organs in the fed- fast state**

Lecture outlines

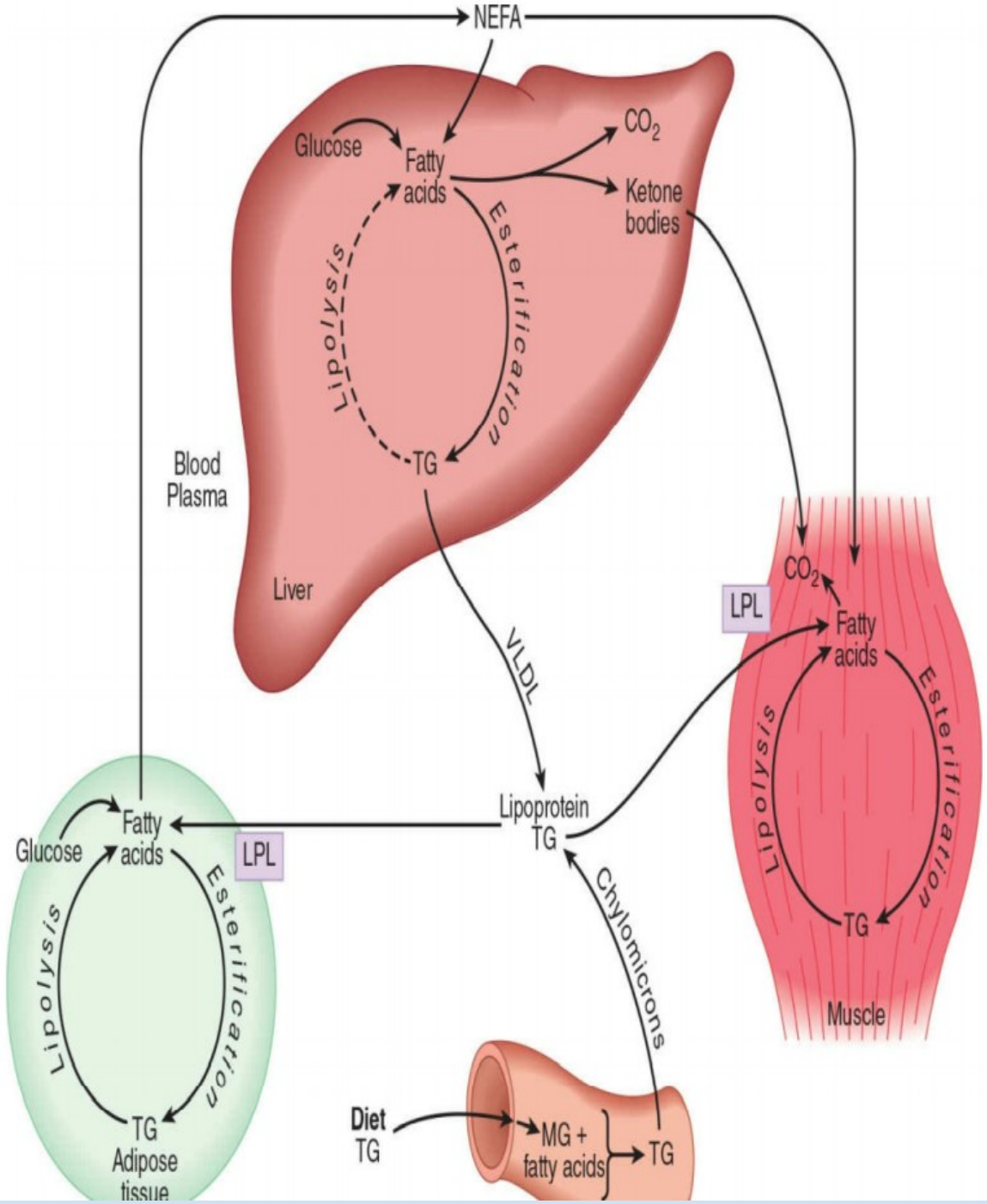
I-Role of liver

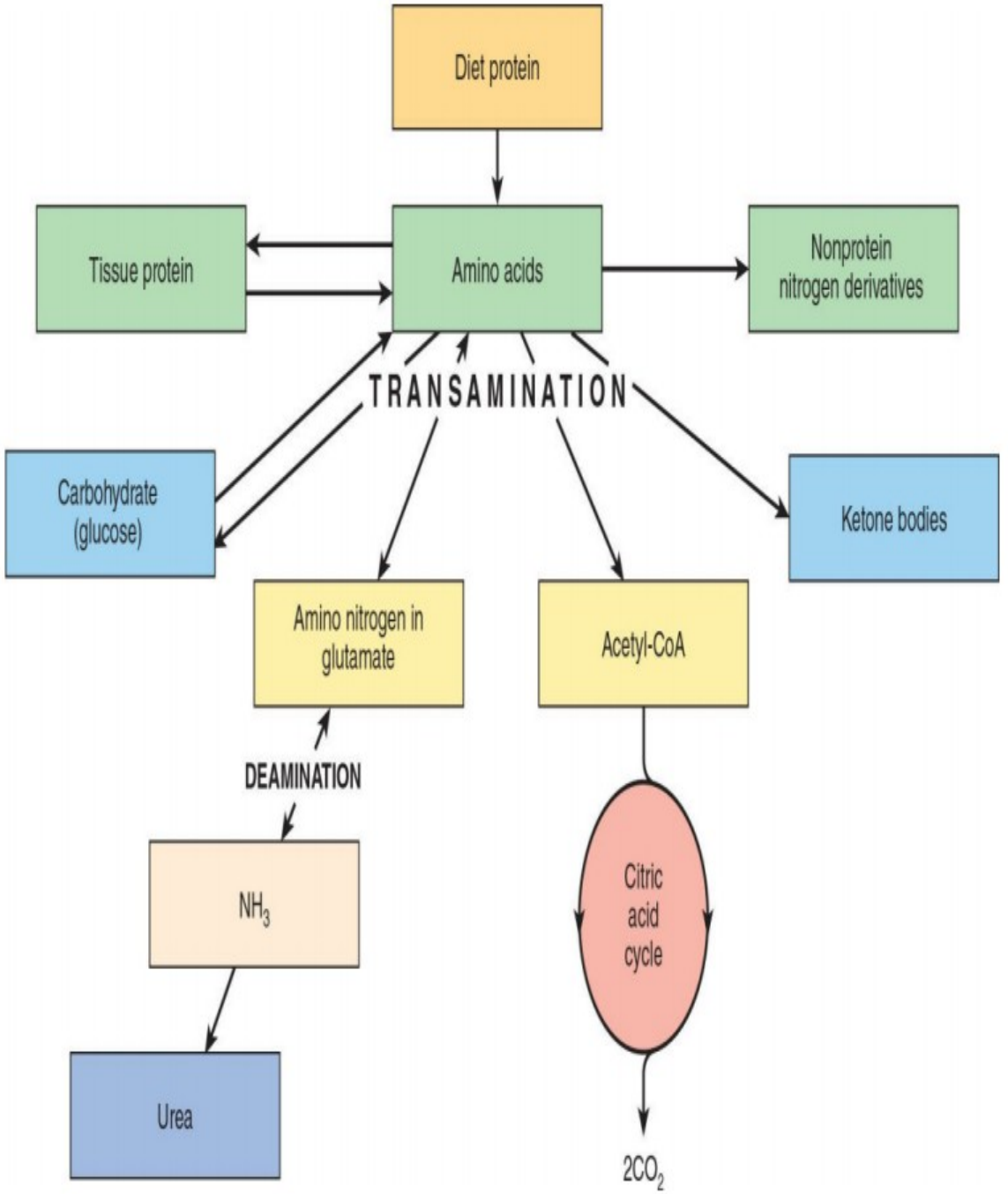
V-Role of Kidney

II-Role of Adipose Tissue

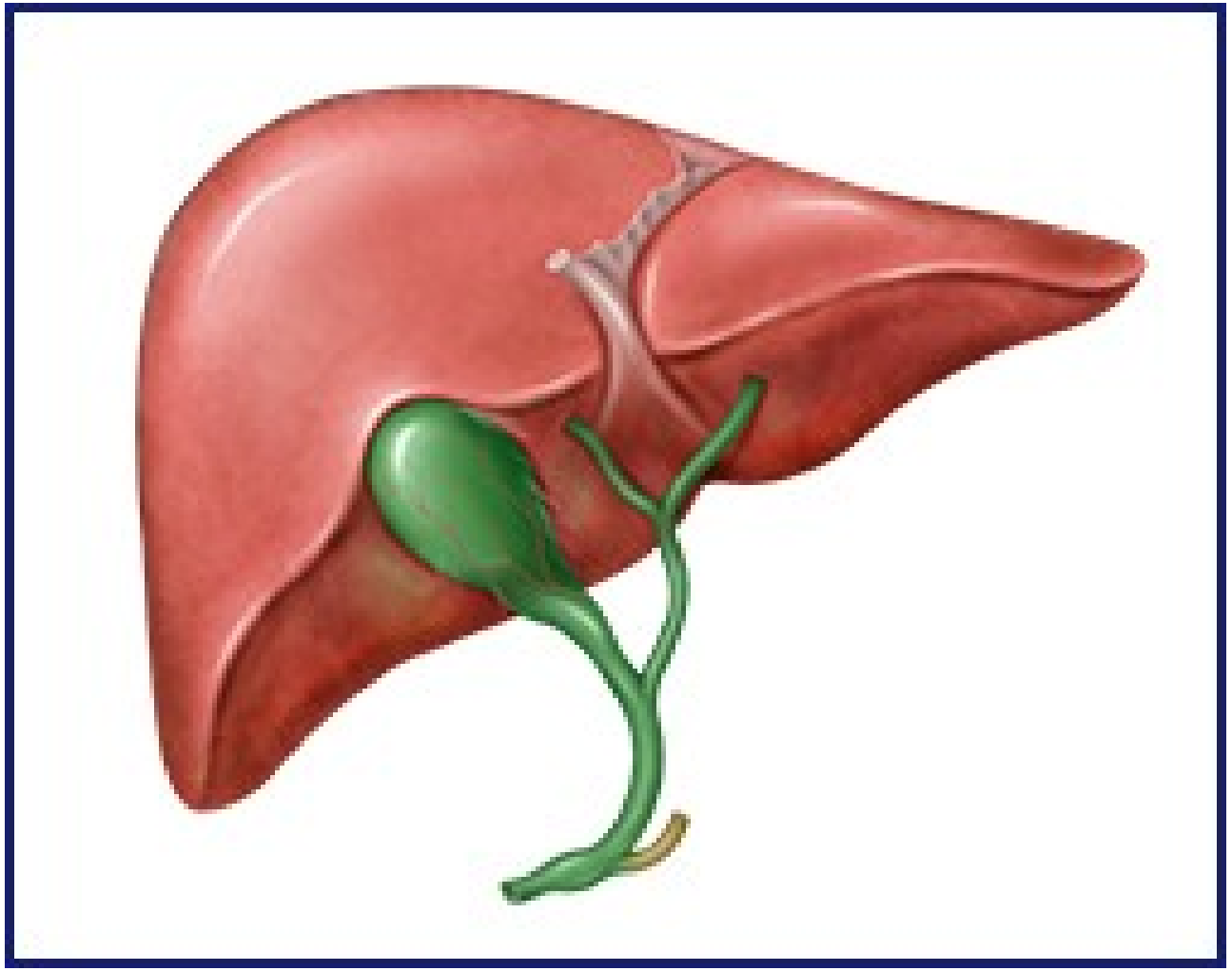
IV-Role of the Brain

III-Role of Skeletal muscles


NEFA
Glucose
Fatty acids
CO_2
Ketone bodies
Lipolysis
Esterification
TG
Blood Plasma
Liver
VLDL
CO_2
LPL
Fatty acids
Lipolysis
Esterification
TG
Muscle
Lipoprotein TG
Chylomicrons
Glucose
Fatty acids
LPL
Lipolysis
Esterification
TG
Adipose tissue
Diet TG
MG + fatty acids
TG


Diet protein
Tissue protein
Amino acids
Nonprotein nitrogen derivatives
TRANSAMINATION
Carbohydrate (glucose)
Ketone bodies
Amino nitrogen in glutamate
Acetyl-CoA
DEAMINATION
NH_3
Citric acid cycle
Urea
$2CO_2$

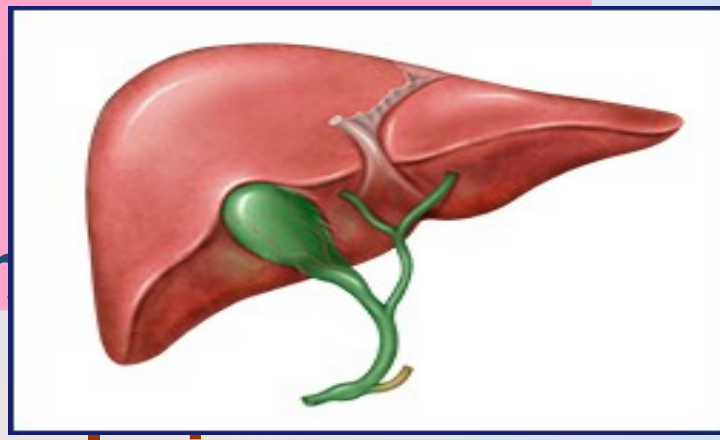
I-Role of liver



I-Role of liver

major site of regulation of blood glucose

(The Nutrient Distributing Center



Well fed

1. **Liver utilize glucose to produce energy via glycolysis**
2. **It store the excess glucose in the form of glycogen by glycogenesis.**

Fasting

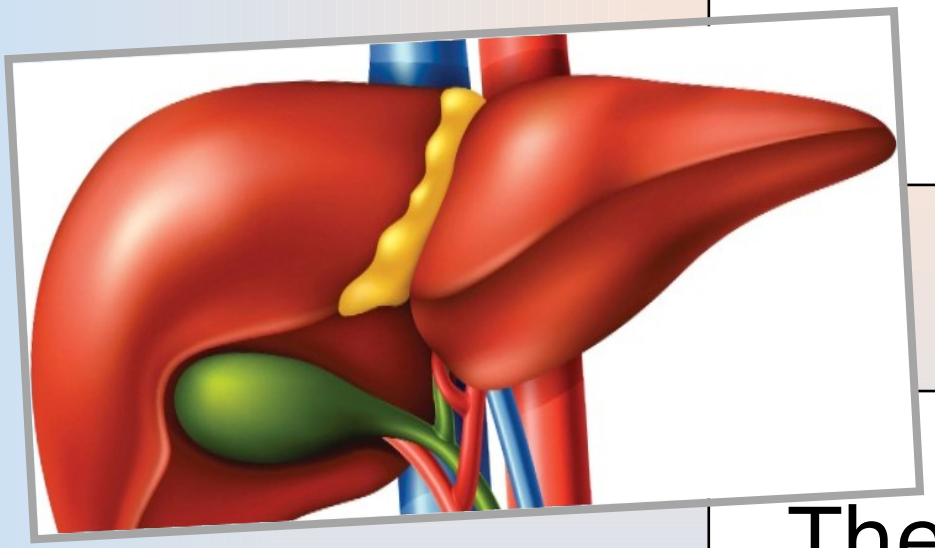
The liver first uses **glycogen degradation**

FOLLOWED BY

The liver uses **gluconeogenesis** to maintain blood glucose levels.

I- **Liver during fasting**
(The Nutrient Distributing Center)

A. Carbohydrate metabolism



The liver first uses **glycogen degradation**

FOLLOWED BY

The liver uses **gluconeogenesis** to maintain blood glucose levels.

1- Increased glycogenolysis:

- ↓ I/G causes rapid mobilization of liver glycogen
- glycogen is nearly exhausted after 10-18 hrs of fasting
- Transient response to early fasting

Increased gluconeogenesis:

- Begins nearly 6 hrs after last meal
- fully active after complete depletion of liver glycogen
- Gluconeogenic precursors (lactate, glycerol & AAs). Energy obtained from fatty acid oxidation from lipolysis
- Important in short & prolonged fasting
- Liver removes amino acids from circulation (proteolysis)
- protein degradation in muscles

Liver glycogen degradation: Liver contains glucose 6- phosphatase which hydrolyzes glucose 6 - phosphate to glucose and Pi (This enzyme is not present in muscles, so liver glycogen replenishes blood glucose not muscles glycogen)

Presence of glucose-6-phosphatase in liver allows release of free Glu to blood both from **glycogenolysis** and **gluconeogenesis**

Increased FAs Oxidation

B. Fat metabolism

- ↑ of lipolysis i.e. mobilization of FAs from adipose tissue to liver
- Subsequent drop in level of malonyl COA due to inactivation of ACC by
- This removes inhibitory effect on CPT-1 allowing B-oxidation to proceed
- FA oxidation provides NADH & ATP required for gluconeogenesis & acetyl COA (stimulator for PC & substrate for KBs

Acetyl COA can’t be used as a substrate for gluconeogenesis?

PDH reaction is irreversible

↑Synthesis of KBs

B. Fat metabolism

Starts during the first days(*3rd day)* of starvation

Favored when

conc. of acetyl-COA produced > oxidative capacity of TCA

Sources of acetyl COA: Oxidation of FAs

The liver is unique in being able to synthesize & release KBs for use by peripheral tissues

Once the level of ketone bodies in the blood is sufficiently high, it ***will inhibit gluconeogenesis especially from proteins (inhibit muscle proteolysis).***

Although protein is an energy source, it is a structural & functional component of body

Only 1/3 of the body's protein can be used for energy production without fatally compromising vital functions

The liver can't use KBs as a fuel lacks thiopherase

. Fatty acids cannot be converted into carbohydrates in the body as the following reaction is not possible

(A) Conversion of glucose-6-phosphate into glucose

(B) Fructose 1, 6-bisphosphate to fructose-6-phosphate

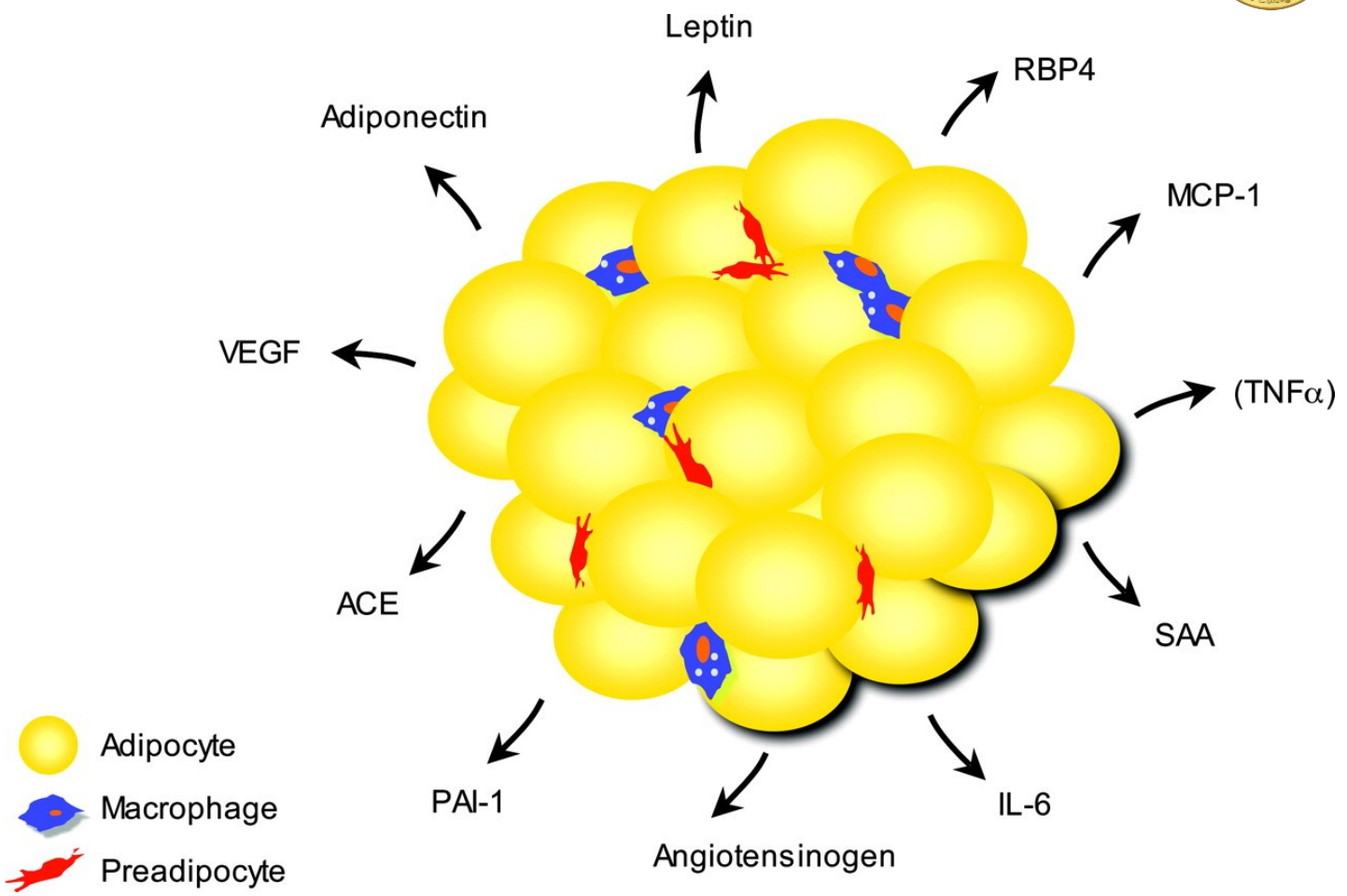
(C) Transformation of acetyl CoA to pyruvate

(D) Formation of acetyl CoA from fatty acids

Stay Safe
And
Let's revise

Marwa Dahpy

II-Role of Adipose Tissue



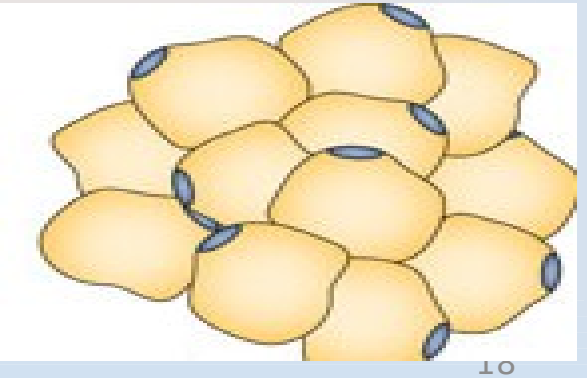
II-Adipose Tissue

- **Well fed:**
- **Increase Glucose transportion by Glu4 increase (insulin dependent)**
- Results in increase **FA synthesis, that stored as TAG** (increase lipogenesis)

- **During fasting:**

Low insulin level, so glucose uptake by ADIPOSE TISSUE is decreased

- Results in decrease in **FA** and **TAG** synthesis



= + of lipolysis

Increased degradation of TAG

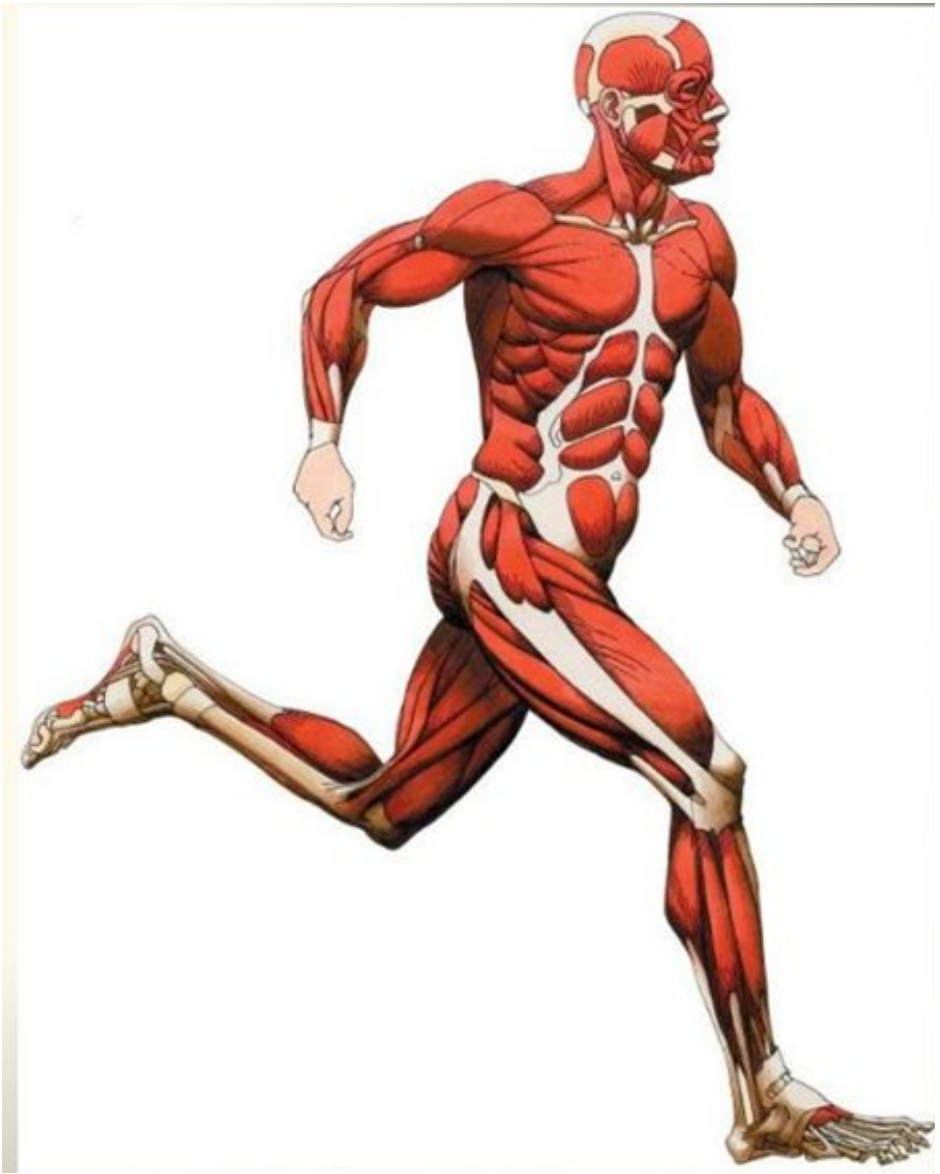
Activation of HSL & subsequent hydrolysis of stored TAG are enhanced by elevated catecholamines

FFAs released are utilized by tissues as a source of energy(B oxidation)

Proionyl CoA from oxidation of odd number FA is gluconeogenic precursor

Glycerol is used as a gluconeogenic precursor by liver (glycerol kinase)

III-Role of Skeletal muscles



III-Skeletal muscles

- **Well fed:**
- **Increase Glucose transportion by Glu4 increase (insulin dependent)**
- **It store glucose as glycogen.**

A.Carbohydrates metabolism

- **During fasting**
- **Low insulin level, so glucose uptake by muscle is decrease**

B. Fat metabolism

2-Concerning lipid metabolism:

During first 2 weeks of fasting

Ms use FAs from adipose tissue & KBs from liver as fuels

After 3 weeks

Oxidizes FAs almost exclusively→ thus sparing KBs for brain

C. Protein metabolism

During the first few days of fasting

- There is a rapid breakdown of muscle protein
- provides amino acids that are used by the liver for gluconeogenesis.

In prolonged starvation, OR in comatose malnourished patients: Respiratory muscles are the most affected with decrease production of antibodies leading to pneumonia and death

C. Protein metabolism

After about three weeks of fasting

- The rate of muscle proteolysis decreases because there is a decline in the need for glucose as a fuel for the brain, which has begun using ketone bodies as a source of energy.

Alanine and glutamine are quantitatively the most important gluconeogenic amino acids released from muscle.

Lecture Quiz

•. In the diet of a diabetic patient, the recommended carbohydrate intake should preferably be in the form of

•(A) Monosaccharides

•(B) Dissaccharides

•(C) Polysaccharides

•(D) All of these

•

Glucose will be converted into fatty acids if the diet has excess of

•(A) Carbohydrates

• (B) Proteins

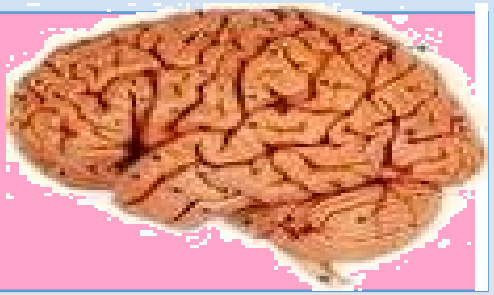
•(C) Fat

•(D) Vitamins

a

IV-Role of the Brain

IV-Brain

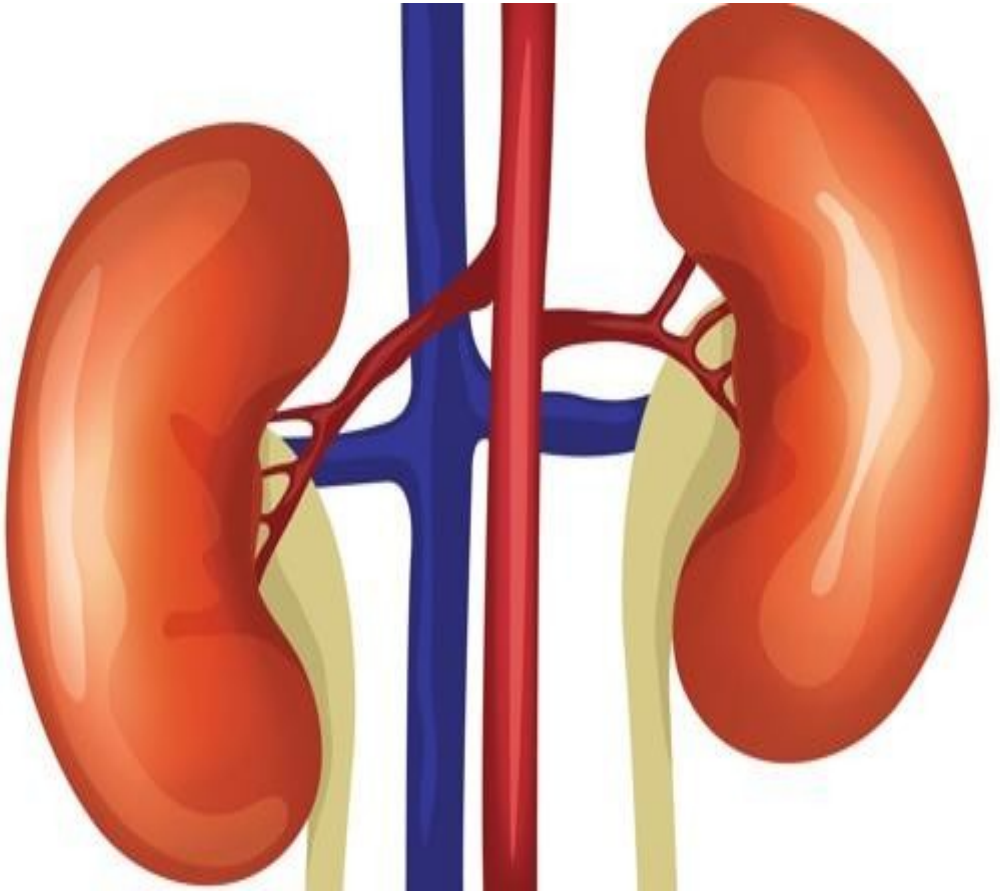


- **Well fed: is a major consumer of glucose**
- **During fasting**

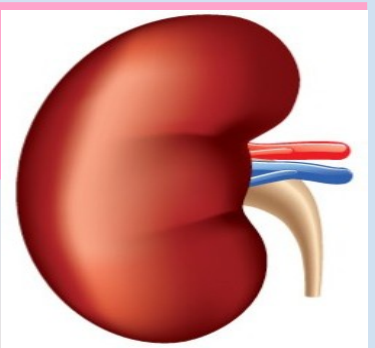
1. During the first few days of fasting: The brain continues to use **glucose**
2. In prolonged fasting

- Plasma ketone bodies reach significantly elevated levels
- So the brain replaces glucose as the primary fuel with ketone bodies.
- This reduces the need for protein catabolism for gluconeogenesis.

V-Role of Kidney



5.Role of the kidney



- Glucose is **continuously filtered** by the glomeruli.
- It is **reabsorbed** by the renal tubules by an ATP-dependant mechanism.
- The capacity of the tubular system to reabsorb glucose is limited to a blood glucose level of **180 mg %.**

- **When blood glucose levels are elevated, the capacity of tubular system for glucose reabsorption is exceeded and glucose passes in urine producing glucosuria.**

- **Glucosuria occurs at glucose concentration exceeding 180 mg %.**

- **This is termed “the renal threshold for glucose*.**

Kidney in Long-Term Fasting

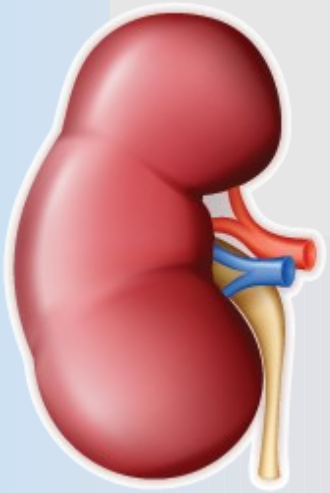
1. Kidney expresses the enzymes of **gluconeogenesis.**

2-The **glutamine** released from the muscle's metabolism is taken up by the kidney

Glutamine acted upon by ***renal glutaminase*** and ***glutamate dehydrogenase***, producing **α-ketoglutarate**, plus **ammonia.**

Kidney in Long-Term Fasting

The **ammonia** picks up **H+** from ketone body dissociation, and is excreted in the urine as **NH4+ ammonium ion**, decreasing the acid load in the body.



- -Kidney also provides compensation for the **acidosis** that accompanies the **increased production of ketone bodies**. Via excess excretion of **NH4**

- **Glucosuria occurs at glucose concentration exceeding -----**
- **This is termed -------.**

SUGGESTED TEXTBOOKS

"Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier.

"Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.

PRAY, EAT
SLEEP, REVISE
& REPEAT
Thank you
Dr.Marwa Dahpy